IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re application of:

Manthorpe, *et. al.*

Appl. No. 09/839,574

Filed: April 23, 2001

For: **Compositions and Methods for *in vivo* Delivery of Polynucleotide-Based Therapeutics**

Confirmation No. 1437

Art Unit: 1635

Examiner: Schnizer, R.

Atty. Docket: 1530.0180002/EKS/EJH

Reply To Restriction Requirement

Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Office Action dated **February 20, 2002**, requesting an election of claims to prosecute in the above-referenced patent application, Applicants hereby provisionally elect to prosecute the invention of Group II , represented by claims 38-53, 88-105, 142-158. It is believed that new claims 164-309, presented in a Preliminary Amendment submitted at the same time as this reply, correspond to Group II. This election is made without prejudice to or disclaimer of the other claims or inventions disclosed.

This election is made **with** traverse.

With respect to the Examiner's division of the claims into two groups and the reasons stated therefor, Applicants respectfully traverse. For example, Groups I and II are related as between a composition of a polynucleotide encoding a polypeptide (Group I) and a method of delivering a polypeptide by administration of a composition of a polynucleotide encoding a polypeptide (Group II).

Even assuming, *arguendo*, that either of Groups I or II represent distinct or independent inventions, Applicants submit that to search and examine the subject matter of all the Groups together would not be a serious burden on the Examiner. For example, publications which disclose the composition of a polynucleotide encoding a polypeptide (Group I) also disclose the method of delivering a polypeptide by administration of a composition of a polynucleotide encoding a polypeptide (Group II). The M.P.E.P. §803 (Eighth Edition, Rev. August, 2001) states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, in view of the M.P.E.P. §803, Applicants respectfully request that all claims be searched and examined in the subject application. Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

Reconsideration and withdrawal of the Restriction Requirement, and consideration and allowance of all pending claims, are respectfully requested.

The Examiner has also required a large number of species elections. Applicants' elections are listed below.

These elections are made **with** traverse.

(a) The Examiner has required an election of species among salts selected from the group consisting of sodium acetate, sodium bicarbonate, sodium sulfate, potassium phosphate, potassium acetate, potassium bicarbonate, potassium sulfate, sodium glycero-phosphate, and sodium glucose-6-phosphate. Applicants hereby provisionally elect to prosecute the species comprising sodium bicarbonate. Claims 1, 58, 110, 164, 175-226,

228-266, and 268-309 are generic to the provisionally elected species. Claim 166 specifically recites the elected species.

(b) The Examiner has appeared to require an election of species from the genus of polypeptides which may be encoded by a polynucleotide. Applicants hereby provisionally elect to prosecute the subgenus of immunogenic polypeptides. Claims 1, 58, 110, 164-184, 190-200, 204-215, 216-232, 238-245, 249-262, 263-278, 284-293, 297-309 are generic to this provisionally elected subgenus. Claims 187, 202, 235, 247, 281, and 295 specifically recite this elected subgenus. Insofar as the examiner requires a more specific election of polypeptide, applicants hereby provisionally elect an immunogenic polypeptide which is a viral polypeptide. Claims 1, 58, 110, 164-184, 187, 190-200, 202, 204-215, 216-232, 235, 238-245, 247, 249-262, 263-278, 281, 284-293, 295, and 297-309 are generic to this provisionally elected subgenus. Insofar as the examiner requires election of a specific polypeptide, applicants hereby provisionally elect the influenza virus nucleoprotein polypeptide. Claims 1, 58, 110, 164-184, 187, 190-200, 202, 204-215, 216-232, 235, 238-245, 247, 249-262, 263-278, 281, 284-293, 295, and 297-309 are generic to this provisionally elected species. The influenza virus nucleoprotein polypeptide is disclosed in paragraph 133 of the specification.

(c) The Examiner has required an election of species among transfection facilitating agents selected from the group consisting of cationic lipids, calcium phosphate, alum, gold, tungsten, peptides, proteins, and polymers. Applicants hereby provisionally elect to prosecute the species comprising cationic lipids. Claims 1, 58, 110, 164-238, and 246-262 are generic to the provisionally elected species. Claims 239-245 and 263-309 specifically recite the elected species.

(d) The Examiner has required an election of species among auxiliary agents selected from the group consisting of surfactants, detergents, polysaccharides, chelators, and DNase inhibitors. Applicants hereby provisionally elect to prosecute the species comprising surfactants. Claims 1, 58, 110, 164-191, 201-216, 226-285, and 294-309 are generic to the provisionally elected species. Claims 192-200, 217-225, and 286-293 specifically recite the elected species.

(e) The Examiner has required an election of species among delivery routes or location. Applicants hereby provisionally elect to prosecute the species comprising muscle and intramuscular delivery. Claims 1, 58, 110, 164-206, 212, 215-251, 261-299, 303 and 307-309 are generic to the provisionally elected species. Claims 209, 210, 213, 214, 255, 256, 259 and 260 specifically recite the provisionally elected species.

Applicants respectfully traverse and request the withdrawal of the requirement for election of species. As a threshold matter, Applicants point out that MPEP § 803 lists the criteria for a proper restriction requirement:

> Under the statute an application may properly be required to be restricted to one of two or more claimed inventions only if they are able to support separate patents and they are either independent (MPEP § 806.04 – § 806.04(i)) or distinct (MPEP § 806.05 – § 806.05(i)).
>
> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, even assuming, *arguendo*, that the groups listed by the Examiner represent patentably distinct species, restriction remains improper unless it can be shown that the search and examination of the listed groups would entail a "serious burden." *See* M.P.E.P. § 803. In the present situation, no such showing has been made. For example,

although the Examiner has asserted that embodiments referring to surfactants, detergents, polysaccharides, chelators, and DNase inhibitors are distinct species, Applicants submit that a search of surfactants as an auxiliary agent would provide useful information regarding detergents, polysaccharides, chelators, and DNase inhibitors as auxiliary agents. Thus, the search and examination of all of the claims of group II would not entail a serious burden.

Applicants assert the right to claim additional embodiments in the event that a generic claim thereto is found to be allowable in accordance with 37 C.F.R. § 1.141(a). Reconsideration and withdrawal of the Requirement for Election of species, and consideration and allowance of all pending claims, are respectfully requested.

Summary

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 19-0036.

Respectfully submitted,

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In re application of:
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Confirmation No.:1437
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Preliminary Amendment

Commissioner for Patents
Washington, D.C. 20231

Sir:

In advance of substantive prosecution, please amend the application as follows. This Amendment is provided in the following format:

(A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;

(B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and

(C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net

addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Claims:

Please cancel claims 2-57, 59-109, 111-163 without prejudice or disclaimer.

Please add the following claims:

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164. (New) A method for delivering a polypeptide to a vertebrate, comprising administering into a tissue or cavity of said vertebrate a composition comprising:

(a) about 1 ng to about 30 mg of a polynucleotide in aqueous solution which operably encodes a polypeptide upon delivery to vertebrate cells *in vivo*;

A1

(b) a salt selected from the group consisting of sodium acetate, sodium bicarbonate, sodium sulfate, potassium phosphate, potassium acetate, potassium bicarbonate, potassium sulfate, sodium glycero-phosphate, sodium glucose-6-phosphate, and reaction, association, or dissociation products thereof;

wherein said salt is dissolved in said aqueous solution at a molar concentration ranging from about 20 mM to about 300 mM; and

wherein said polypeptide is expressed in the vertebrate in an amount sufficient to be detectable.

165. (New) The method of claim 164, wherein said salt is sodium acetate or reaction, association, or dissociation products thereof.

166. (New) The method of claim 164, wherein said salt is sodium bicarbonate or reaction, association, or dissociation products thereof.

167. (New) The method of claim 164, wherein said salt is sodium sulfate or reaction, association, or dissociation products thereof.

A1 cont'd

168. (New) The method of claim 164, wherein said salt is sodium acetate or reaction, association, or dissociation products thereof.

169. (New) The method of claim 164, wherein said salt is potassium phosphate or reaction, association, or dissociation products thereof.

170. (New) The method of claim 164, wherein said salt is potassium acetate or reaction, association, or dissociation products thereof.

171. (New) The method of claim 164, wherein said salt is potassium bicarbonate or reaction, association, or dissociation products thereof.

172. (New) The method of claim 164, wherein said salt is potassium sulfate or reaction, association, or dissociation products thereof.

173. (New) The method of claim 164, wherein said salt is sodium glycero-phosphate or reaction, association, or dissociation products thereof.

174. (New) The method of claim 164, wherein said salt is sodium glucose-6-phosphate or reaction, association, or dissociation products thereof.

175. (New) The method of claim 164, wherein said salt is present at a molar concentration of about 100 mM to about 200 mM.

A1 cont'd

176. (New) The method of claim 164, wherein said salt is present at a molar concentration of about 150 mM.

177. (New) The method of claim 175, further comprising chloride ion in said aqueous solution at a molar equivalent concentration of zero (0) mM to about 125 mM, and reaction, association, or dissociation products thereof.

178. (New) The method of claim 177, comprising chloride ion at a molar equivalent concentration from 0 mM to about 10 mM.

179. (New) The method of claim 178, which is substantially free of chloride ion.

180. (New) The method of claim 164, wherein said polynucleotide is DNA operably associated with a promoter.

181. (New) The method of claim 180, wherein said polynucleotide is contained in a plasmid.

182. (New) The method of claim 164, wherein said polynucleotide is RNA.

183. (New) The method of claim 182, wherein said polynucleotide is contained in messenger RNA.

A 1 cont'd

184. (New) The method of claim 164, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an antigenic polypeptide, an immunogenic polypeptide, an immunomodulatory polypeptide, and a functional self polypeptide.

185. (New) The method of 184, wherein said therapeutic polypeptide is selected from the group consisting of granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, *Leishmania* elongation initiating factor, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic

factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, insulin, and therapeutically active fragments, analogs, or derivatives thereof.

186. (New) The method of claim 184, wherein said antigenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and antigenic fragments, derivatives, or analogs thereof.

A1 cont'd

187. (New) The method of claim 184, wherein said immunogenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and immunogenic fragments, derivatives, or analogs thereof.

188. (New) The method of claim 184, wherein said immunomodulatory polypeptide is selected from the group consisting of a cytokine, a chemokine, and fragments, derivatives, or analogs thereof having immunomodulatory activity.

189. (New) The method of claim 184, wherein said functional self polypeptide is selected from the group consisting of insulin, dystrophin, cystic fibrosis transmembrane conductance regulator, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15,

interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, and therapeutically active fragments, analogs, or derivatives thereof.

A 1 cont'd

190. (New) The method of claim 164, further comprising a transfection facilitating agent selected from the group consisting of calcium phosphate, gold, tungsten, or other metal particles, transfection facilitating peptides, transfection facilitating proteins, and transfection facilitating polymers.

191. (New) The method of claim 164, further comprising an auxiliary agent selected from the group consisting of a surfactant, a detergent, a polysaccharide, a chelator, a DNase inhibitor, and a condensing agent.

192. (New) The method of claim 191, wherein said auxiliary agent selected from the group consisting of Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® F127, Pluronic® P65, Pluronic® P85, Pluronic® F103, Pluronic® P104, Pluronic® P105, Pluronic® P123, Pluronic® L31, Pluronic® L43, Pluronic® L44, Pluronic® L61, Pluronic® L62, Pluronic® L64, Pluronic® L81, Pluronic® L92, Pluronic® L101,

Pluronic® L121, Pluronic® R 17R4, Pluronic® R 25R4, Pluronic® R 25R2, IGEPAL CA 630®, NONIDET NP-40, Nonidet ® P40, Tween-20®, Tween-80®, Triton X-100™, Triton X-114™, Thesit®; sodium dodecyl sulfate (SDS); stachyose; dimethylsulfoxide (DMSO); and EDTA.

193. (New) The method of claim 192, wherein said auxiliary agent is selected from the group consisting of Nonidet® P40, Triton X-100™, Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic® L92, Pluronic® R 17R4, Pluronic® R 25R4 and Pluronic® R 25R2.

A1 cont'd

194. (New) The method of claim 193, wherein said auxiliary agent is Pluronic® R 25R2.

195. (New) The method of claim 193, comprising an amount of auxiliary agent selected from the group consisting of about about 0.01% (v/v) to about 0.1% (v/v) of NONIDET NP-40®; about 0.006% (v/v) to about 0.1% (v/v) of Triton X-100™; about 0.1% (w/v) to about 6.0% (w/v) of Pluronic® F68; about 0.001% (w/v) to about 2.0% (w/v) of Pluronic® F77; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F108; about 0.01% (w/v) to about 1% (w/v) Pluronic® P65; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F103; about 0.0005% (w/v) to about 1.0% (w/v) of Pluronic® L44; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® L64; about 0.002% (w/v) to about

1.0% (w/v) of Pluronic® R 17R4; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

196. (New) The method of claim 195, comprising about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

197. (New) The method of claim 195, comprising an amount of auxiliary agent selected from the group consisting of about 0.01% (v/v) to about 0.05% (v/v) of NONIDET N-P 40®; about 0.01% (v/v) to about 0.03% (v/v) of Triton X-100™; about 0.5% to about 4.0% (w/v) of Pluronic® F68; about 0.1% (w/v) to about 1.7% (w/v) of Pluronic® F77; about 0.05% (w/v) to about 0.5% (w/v) of Pluronic® F108, about 0.1% (w/v) to about 1% (w/v) of Pluronic® P65; about 0.05% (w/v) to about 0.10% (w/v) of Pluronic® F103; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L31; about 0.001% (w/v) to about 0.10% (w/v) of Pluronic® L44; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L61; about 0.01% (w/v) to about 0.5% (w/v) of Pluronic® L64; about 0.001 % (w/v) to about 1.0% (w/v) Pluronic® L92; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 17R4; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

A1 cont'd

198. (New) The method of claim 195, comprising about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

199. (New) The method of claim 195, comprising an amount of auxiliary agent selected from the group consisting of 0.01% NONIDET NP-40®; 0.01% (v/v) Triton X-100™; 4% Pluronic® F68; 1.0% (w/v) Pluronic® F77; 0.1% (w/v) of Pluronic® F108; 0.5% (w/v) of Pluronic® P65; 0.05% (w/v) of Pluronic® F103; 0.05% (w/v) of Pluronic® L31; 0.001% (w/v) of Pluronic® L44; 0.01% (w/v) of Pluronic® L61; about 0.01% (w/v) to about 0.1% (w/v) of Pluronic® L64; 0.05% (w/v) of Pluronic® L92; 0.10% (w/v) of Pluronic® R 17R4; 0.01% (w/v) of Pluronic® R 25R4; and 0.01% (w/v) of Pluronic® R 25R2.

A 1 cont'd

200. (New) The method of claim 196, comprising 0.01% (w/v) of Pluronic® R 25R2.

201. (New) The method of claim 164;

wherein said polypeptide is a therapeutic polypeptide;

wherein said vertebrate is in need of the therapy provided by said polypeptide; and

wherein said therapeutic polypeptide is expressed in the vertebrate in a therapeutically effective amount.

202. (New) The method of claim 164,

wherein said polypeptide is an immunogenic or immunomodulatory polypeptide;

wherein said vertebrate is in need of such an enhanced or modulated immune response provided by said polypeptide; and

wherein said immunogenic or immunomodulatory polypeptide is expressed in the vertebrate in a sufficient amount to induce a desired immune response.

203. (New) The method of claim 164,

wherein said polypeptide is a functional self polypeptide;

wherein said vertebrate is incapable of making a sufficient amount of said polypeptide; and

wherein said functional self polypeptide is expressed in the vertebrate in a sufficient amount to supply the vertebrate's requirements for said polypeptide.

A1 cont'd

204. (New) The method of claim 164, wherein said vertebrate is a mammal.

205. (New) The method of claim 204, wherein said mammal is a human.

206. (New) The method of claim 164, wherein said tissue is selected from the group consisting of muscle, skin, brain tissue, lung tissue, liver tissue, spleen tissue, bone marrow tissue, thymus tissue, heart tissue, lymph tissue, blood tissue, bone tissue, connective tissue, mucosal tissue, pancreas tissue, kidney tissue, gall bladder tissue, intestinal tissue, testicular tissue, ovarian tissue, uterine tissue, vaginal tissue, rectal tissue, nervous system tissue, eye tissue, glandular tissue, and tongue tissue.

207. (New) The method of claim 164, wherein said cavity is selected from the group consisting of the lungs, the mouth, the nasal cavity, the stomach, the peritoneal cavity, the intestine, a heart chamber, veins, arteries, capillaries, lymphatic cavities, the uterine cavity, the vaginal cavity, the rectal cavity, joint cavities, ventricles in brain, spinal canal in spinal cord, and the ocular cavities.

208. (New) The method of claim 196, wherein said cavity comprises a mucosal surface.

A1 cont'd

209. (New) The method of claim 206, wherein said tissue is muscle.

210. (New) The method of claim 209, wherein said tissue is skeletal muscle, smooth muscle, or myocardium.

211. (New) The method of claim 164, wherein said administration is intravenous.

212. (New) The method of claim 164, wherein said administration is by a route selected from the group consisting of intramuscular, intratracheal, intranasal, transdermal, interdermal, subcutaneous, intraocular, vaginal, rectal, intraperitoneal, intraintestinal and inhalation.

213. (New) The method of claim 164, wherein said administration route is intramuscular.

214. (New) The method of claim 213, wherein said administration is by intramuscular injection.

215. (New) A method of reducing the amount of polynucleotide required to obtain a desired clinical response in a vertebrate, comprising administering to the vertebrate the composition of claim 164.

A 1 cont'd

~~216.~~ (New) A method for delivering a polypeptide to a vertebrate, comprising administering into a tissue or cavity of said vertebrate a composition comprising:

(a) about 1 ng to about 30 mg of a polynucleotide which operably encodes a polypeptide upon delivery to vertebrate cells *in vivo*;

(b) an auxiliary agent selected from the group consisting of a surfactant, a detergent, a polysaccharide, a chelator, a DNase inhibitor, a condensing agent, combinations thereof, and reaction, association and dissociation products thereof; and

(c) water;

wherein said polypeptide is expressed in the vertebrate in an amount sufficient to be detectable.

217. (New) The method of claim 216, wherein said auxiliary agent is selected from the group consisting of Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® F127, Pluronic® P65, Pluronic® P85, Pluronic® F103, Pluronic® P104, Pluronic® P105, Pluronic® P123, Pluronic® L31, Pluronic® L43, Pluronic® L44, Pluronic® L61,

Pluronic® L62, Pluronic® L64, Pluronic® L81, Pluronic® L92, Pluronic® L101, Pluronic® L121, Pluronic® R 17R4, Pluronic® R 25R4, Pluronic® R 25R2, IGEPAL CA 630®, NONIDET NP-40, Nonidet ® P40, Tween-20®, Tween-80®, Triton X-100™, Triton X-114™, Thesit®; sodium dodecyl sulfate (SDS); stachyose; dimethylsulfoxide (DMSO); and EDTA.

218. (New) The method of claim 217, wherein said auxiliary agent is selected from the group consisting of Nonidet® P40, Triton X-100™, Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic® L92, Pluronic® R 17R4, Pluronic® R 25R4 and Pluronic® R 25R2.

219. (New) The method of claim 218, wherein said auxiliary agent is Pluronic® R 25R2.

220. (New) The method of claim 218, comprising an amount of auxiliary agent selected from the group consisting of about about 0.01% (v/v) to about 0.1% (v/v) of NONIDET NP-40®; about 0.006% (v/v) to about 0.1% (v/v) of Triton X-100™; about 0.1% (w/v) to about 6.0% (w/v) of Pluronic® F68; about 0.001% (w/v) to about 2.0% (w/v) of Pluronic® F77; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F108; about 0.01% (w/v) to about 1% (w/v) Pluronic® P65; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F103; about 0.0005% (w/v) to about 1.0% (w/v) of Pluronic® L44; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® L64; about 0.002% (w/v) to about

1.0% (w/v) of Pluronic® R 17R4; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

221. (New) The method of claim 220, comprising about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

222. (New) The method of claim 220, comprising an amount of auxiliary agent selected from the group consisting of about 0.01% (v/v) to about 0.05% (v/v) of NONIDET N-P 40®; about 0.01% (v/v) to about 0.03% (v/v) of Triton X-100™; about 0.5% to about 4.0% (w/v) of Pluronic® F68; about 0.1% (w/v) to about 1.7% (w/v) of Pluronic® F77; about 0.05% (w/v) to about 0.5% (w/v) of Pluronic® F108, about 0.1% (w/v) to about 1% (w/v) of Pluronic® P65; about 0.05% (w/v) to about 0.10% (w/v) of Pluronic® F103; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L31; about 0.001% (w/v) to about 0.10% (w/v) of Pluronic® L44; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L61; about 0.01% (w/v) to about 0.5% (w/v) of Pluronic® L64; about 0.001 % (w/v) to about 1.0% (w/v) Pluronic® L92; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 17R4; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

A1 cont'd

223. (New) The method of claim 222, comprising about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

224. (New) The method of claim 220, comprising an amount of auxiliary agent selected from the group consisting of 0.01% NONIDET NP-40®; 0.01% (v/v) Triton X-100™; 4% Pluronic® F68; 1.0% (w/v) Pluronic® F77; 0.1% (w/v) of Pluronic® F108; 0.5% (w/v) of Pluronic® P65; 0.05% (w/v) of Pluronic® F103; 0.05% (w/v) of Pluronic® L31; 0.001% (w/v) of Pluronic® L44; 0.01% (w/v) of Pluronic® L61; about 0.01% (w/v) to about 0.1% (w/v) of Pluronic® L64; 0.05% (w/v) of Pluronic® L92; 0.10% (w/v) of Pluronic® R 17R4; 0.01% (w/v) of Pluronic® R 25R4; and 0.01% (w/v) of Pluronic® R 25R2.

A1 cont'd

225. (New) The method of claim 224, comprising 0.01% (w/v) of Pluronic® R 25R2.

226. (New) The method of claim 216, further comprising a salt M-X wherein M is a cation selected from the group consisting of sodium and potassium, and wherein X is an anion selected from the group consisting of phosphate, acetate, bicarbonate, sulfate, and pyruvate.

227. (New) The method of claim 226, wherein said salt is sodium phosphate or potassium phosphate.

228. (New) The method of claim 216, wherein said polynucleotide is DNA operably associated with a promoter.

229. (New) The method of claim 228, wherein said polynucleotide is contained on a plasmid.

230. (New) The method of claim 216, wherein said polynucleotide is RNA.

231. (New) The method of claim 230, wherein said polynucleotide is contained in messenger RNA.

A1 cont'd

232. (New) The method of claim 216, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an antigenic polypeptide, an immunogenic polypeptide, an immunomodulatory polypeptide, and a functional self polypeptide.

233. (New) The method of claim 232, wherein said therapeutic polypeptide is selected from the group consisting of granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, *Leishmania* elongation initiating factor, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-

derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, insulin, and therapeutically active fragments, analogs, or derivatives thereof.

234. (New) The method of claim 232, wherein said antigenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergen, a tumor specific polypeptide and antigenic fragments, analogs, or derivatives thereof.

A 1 cont'd

235. (New) The method of claim 232, wherein said immunogenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergen, a tumor specific polypeptide, and immunogenic fragments, analogs, or derivatives thereof.

236. (New) The method of claim 232, wherein said immunomodulatory polypeptide is selected from the group consisting of a cytokine, a chemokine, and immunomodulatory fragments, analogs, or derivatives thereof.

237. (New) The method of claim 232, wherein said functional self polypeptide is selected from the group consisting of insulin, dystrophin, cystic fibrosis transmembrane conductance regulator, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega,

interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, and therapeutically active fragments, analogs,and derivatives thereof.

A1 cont'd

238. (New) The method of claim 216, further comprising a transfection facilitating agent selected from the group consisting of cationic lipids, calcium phosphate, alum, gold, tungsten, or other metal particles, transfection facilitating peptides, transfection facilitating proteins, and transfection facilitating polymers.

239. (New) The method of claim 238, wherein said transfection facilitating agent is a cationic lipid.

240. (New) The method of claim 239, wherein said cationic lipid is selected from the group consisting of DMRIE, GAP-DMORIE and GAP-DLRIE.

241. (New) The method of claim 239, wherein said cationic lipid further comprises one or more co-lipids.

242. (New) The method of claim 241, wherein said co-lipids are selected from the group consisting of DOPE, DPyPE, and DMPE.

243. (New) The method of claim 242, comprising GAP-DLRIE and DOPE.

244. (New) The method of claim 241, wherein the cationic lipid:co-lipid molar ratio ranges from about 2:1 to 1:2.

245. (New) The method of claim 244, wherein the cationic lipid:co-lipid molar ratio is about 1:1.

A1 cont'd

246. (New) The method of claim 216;

wherein said polypeptide is a therapeutic polypeptide;

wherein said vertebrate is in need of the therapy provided by said polypeptide; and

wherein said therapeutic polypeptide is expressed in the vertebrate in a therapeutically effective amount.

247. (New) The method of claim 216,

wherein said polypeptide is an immunogenic or immunomodulatory polypeptide;

wherein said vertebrate is in need of such an enhanced or modulated immune response provided by said polypeptide; and

wherein said immunogenic or immunomodulatory polypeptide is expressed in the vertebrate in a sufficient amount to induce a desired immune response.

248. (New) The method of claim 216,

wherein said polypeptide is a functional self polypeptide;

wherein said vertebrate is incapable of making a sufficient amount of said polypeptide; and

wherein said functional self polypeptide is expressed in the vertebrate in a sufficient amount to supply the vertebrate's requirements for said polypeptide.

249. (New) The method of claim 216, wherein said vertebrate is a mammal.

A 1 cont'd

250. (New) The method of claim 249, wherein said mammal is a human.

251. (New) The method of claim 216, wherein said tissue is selected from the group consisting of muscle, skin, brain tissue, lung tissue, liver tissue, spleen tissue, bone marrow tissue, thymus tissue, heart tissue, lymph tissue, blood tissue, bone tissue, connective tissue, mucosal tissue, pancreas tissue, kidney tissue, gall bladder tissue, intestinal tissue, testicular tissue, ovarian tissue, uterine tissue, vaginal tissue, rectal tissue, nervous system tissue, eye tissue, glandular tissue, and tongue tissue.

252. (New) The method of claim 216, wherein said cavity is selected from the group consisting of the lungs, the mouth, the nasal cavity, the stomach, the peritoneal cavity, the intestine, a heart chamber, veins, arteries, capillaries, lymphatic cavities, the uterine cavity, the vaginal cavity, the rectal cavity, joint cavities, ventricles in brain, spinal canal in spinal cord, and the ocular cavities.

253. (New) The method of claim 216, wherein said cavity comprises a mucosal surface.

254. (New) The method of claim 253, wherein said mucosal surface is lung tissue.

255. (New) The method of claim 251, wherein said tissue is muscle.

A 1 contd

256. (New) The method of claim 255, wherein said tissue is skeletal muscle, smooth muscle, or myocardium.

257. (New) The method of claim 216, wherein said administration is by a route selected from the group consisting of intramuscular, intravenous, intratracheal, intranasal, transdermal, interdermal, subcutaneous, intraocular, vaginal, rectal, intraperitoneal, intraintestinal and inhalation.

258. (New) The method of claim 216, wherein said administration route is intravenous.

259. (New) The method of claim 216, wherein said administration route is intramuscular.

260. (New) The method of claim 259, wherein said administration is by intramuscular injection.

261. (New) The method of claim 216, wherein said administration is mediated by a catheter.

262. (New) A method of reducing the amount of polynucleotide required to obtain a desired clinical response in a vertebrate, comprising administering to the vertebrate the composition of claim 216.

A 1 cont'd

~~263.~~ (New) A method for delivering a polypeptide into a vertebrate, comprising administering into a tissue or cavity of said vertebrate a composition comprising:

(a) about 1 ng to about 30 mg of a polynucleotide in aqueous solution which operably encodes a polypeptide upon delivery to vertebrate cells *in vivo*, wherein said polynucleotide is complexed with a cationic lipid;

(b) a salt M-X dissolved in said aqueous solution at a molar concentration ranging from about 0.1 mM to about 50 mM, and reaction, association, and dissociation products thereof, wherein M is a cation selected from the group consisting of sodium and potassium, wherein X is an anion selected from the group consisting of phosphate, acetate, bicarbonate, sulfate, and pyruvate; and wherein said aqueous solution is substantially free of chloride anion;

wherein said aqueous solution is substantially free of chloride anion, and wherein said polypeptide is expressed in the vertebrate in an amount sufficient to be detectable.

264. (New) The method of claim 263, wherein M-X is present at a molar concentration of about 1 mM to about 20 mM.

265. (New) The method of claim 264, wherein M-X is present at a molar concentration of about 1 mM to about 5 mM.

266. (New) The method of claim 265, wherein M-X is present at a molar concentration of about 2.5 mM.

A 1 cont'd

267. (New) The method of claim 263, wherein M is sodium or potassium, and X is phosphate.

268. (New) The method of claim 263, wherein said cationic lipid is selected from the group consisting of DMRIE, GAP-DMORIE and GAP-DLRIE.

269. (New) The method of claim 263, wherein said cationic lipid further comprises one or more co-lipids.

270. (New) The method of claim 269, wherein said co-lipids are selected from the group consisting of DOPE, DPyPE, and DMPE.

271. (New) The method of claim 270, comprising GAP-DLRIE and DOPE.

272. (New) The method of claim 269, wherein the cationic lipid:co-lipid molar ratio ranges from about 2:1 to 1:2.

273. (New) The method of claim 272, wherein the cationic lipid:co-lipid molar ratio is about 1:1.

274. (New) The method of claim 263, wherein said polynucleotide is DNA operably associated with a promoter

A 1 cont'd

275. (New) The method of claim 274, wherein said polynucleotide is contained on a plasmid.

276. (New) The method of claim 263, wherein said polynucleotide is RNA.

277. (New) The method of claim 276, wherein said polynucleotide is contained in messenger RNA.

278. (New) The method of claim 263, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an antigenic polypeptide, an immunogenic polypeptide, an immunomodulatory polypeptide, and a functional self polypeptide.

279. (New) The method of claim 278, wherein said therapeutic polypeptide is selected from the group consisting of granulocyte macrophage colony stimulating factor,

granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, Leishmania elongation initiating factor, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, insulin, and therapeutically active fragments, derivatives, and analogs thereof.

A1 cont'd

280. (New) The method of claim 278, wherein said antigenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and antigenic fragments, analogs, and derivatives thereof.

281. (New) The method of claim 278, wherein said immunogenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and immunogenic fragments, analogs, and derivatives thereof.

282. (New) The method of claim 278, wherein said immunomodulatory polypeptide is selected from the group consisting of a cytokine, a chemokine, and immunomodulatory fragments, analogs, or derivatives thereof.

283. (New) The method of claim 278, wherein said functional self polypeptide is selected from the group consisting of insulin, dystrophin, cystic fibrosis transmembrane conductance regulator, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, and therapeutically active fragments, analogs, or derivatives thereof.

A1 cont'd

284. (New) The method of claim 263, further comprising a transfection facilitating agent selected from the group consisting of calcium phosphate, alum, gold, tungsten, or other metal particles, transfection facilitating peptides, transfection facilitating proteins, and transfection facilitating polymers.

285. (New) The method of claim 263, further comprising an auxiliary agent selected from the group consisting of a surfactant, a detergent, a polysaccharide, a chelator, a DNase inhibitor, and a condensing agent.

286. (New) The method of claim 285, wherein said auxiliary agent selected from the group consisting of Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® F127, Pluronic® P65, Pluronic® P85, Pluronic® F103, Pluronic® P104, Pluronic® P105, Pluronic® P123, Pluronic® L31, Pluronic® L43, Pluronic® L44, Pluronic® L61, Pluronic® L62, Pluronic® L64, Pluronic® L81, Pluronic® L92, Pluronic® L101, Pluronic® L121, Pluronic® R 17R4, Pluronic® R 25R4, Pluronic® R 25R2, IGEPAL CA 630®, NONIDET NP-40, Nonidet ® P40, Tween-20®, Tween-80®, Triton X-100™, Triton X-114™, Thesit®; sodium dodecyl sulfate (SDS); stachyose; dimethylsulfoxide (DMSO); and EDTA.

A 1 cont'd

287. (New) The method of claim 286, wherein said auxiliary agent is selected from the group consisting of Nonidet® P40, Triton X-100™, Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic® L92, Pluronic® R 17R4, Pluronic® R 25R4 and Pluronic® R 25R2.

288. (New) The method of claim 287, wherein said auxiliary agent is Pluronic® R 25R2.

289. (New) The method of claim 287, comprising an amount of auxiliary agent selected from the group consisting of about about 0.01% (v/v) to about 0.1% (v/v) of NONIDET NP-40®; about 0.006% (v/v) to about 0.1% (v/v) of Triton X-100™; about 0.1% (w/v) to about 6.0% (w/v) of Pluronic® F68; about 0.001% (w/v) to about 2.0% (w/v) of Pluronic® F77; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F108; about 0.01% (w/v) to about 1% (w/v) Pluronic® P65; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F103; about 0.0005% (w/v) to about 1.0% (w/v) of Pluronic® L44; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® L64; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 17R4; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

A 1 cont'd

290. (New) The method of claim 289, comprising about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

291. (New) The method of claim 289, comprising an amount of auxiliary agent selected from the group consisting of about 0.01% (v/v) to about 0.05% (v/v) of NONIDET N-P 40®; about 0.01% (v/v) to about 0.03% (v/v) of Triton X-100™; about 0.5% to about 4.0% (w/v) of Pluronic® F68; about 0.1% (w/v) to about 1.7% (w/v) of Pluronic® F77; about 0.05% (w/v) to about 0.5% (w/v) of Pluronic® F108, about 0.1% (w/v) to about 1% (w/v) of Pluronic® P65; about 0.05% (w/v) to about 0.10% (w/v) of Pluronic® F103; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L31; about 0.001% (w/v) to about 0.10% (w/v) of Pluronic® L44; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L61; about 0.01% (w/v) to about 0.5% (w/v) of Pluronic® L64;

about 0.001 % (w/v) to about 1.0% (w/v) Pluronic® L92; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 17R4; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

292. (New) The method of claim 291, comprising about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

A' contd

293. (New) The method of claim 291, comprising an amount of auxiliary agent selected from the group consisting of 0.01% NONIDET NP-40®; 0.01% (v/v) Triton X-100™; 4% Pluronic® F68; 1.0% (w/v) Pluronic® F77; 0.1% (w/v) of Pluronic® F108; 0.5% (w/v) of Pluronic® P65; 0.05% (w/v) of Pluronic® F103; 0.05% (w/v) of Pluronic® L31; 0.001% (w/v) of Pluronic® L44; 0.01% (w/v) of Pluronic® L61; about 0.01% (w/v) to about 0.1% (w/v) of Pluronic® L64; 0.05% (w/v) of Pluronic® L92; 0.10% (w/v) of Pluronic® R 17R4; 0.01% (w/v) of Pluronic® R 25R4; and 0.01% (w/v) of Pluronic® R 25R2.

294. (New) The method of claim 263;

wherein said polypeptide is a therapeutic polypeptide;

wherein said vertebrate is in need of the therapy provided by said polypeptide; and

wherein said therapeutic polypeptide is expressed in the vertebrate in a therapeutically effective amount.

295. (New) The method of claim 263,

wherein said polypeptide is an immunogenic or immunomodulatory polypeptide;

wherein said vertebrate is in need of such an enhanced or modulated immune response provided by said polypeptide; and

wherein said immunogenic or immunomodulatory polypeptide is expressed in the vertebrate in a sufficient amount to induce a desired immune response.

296. (New) The method of claim 263,

wherein said polypeptide is a functional self polypeptide;

wherein said vertebrate is incapable of making a sufficient amount of said polypeptide; and

wherein said functional self polypeptide is expressed in the vertebrate in a sufficient amount to supply the vertebrate's requirements for said polypeptide.

297. (New) The method of claim 263, wherein said vertebrate is a mammal.

298. (New) The method of claim 263, wherein said mammal is a human.

299. (New) The method of claim 263, wherein said tissue is selected from the group consisting of muscle, skin, brain tissue, lung tissue, liver tissue, spleen tissue, bone marrow tissue, thymus tissue, heart tissue, lymph tissue, blood tissue, bone tissue, connective tissue, mucosal tissue, pancreas tissue, kidney tissue, gall bladder tissue,

intestinal tissue, testicular tissue, ovarian tissue, uterine tissue, vaginal tissue, rectal tissue, nervous system tissue, eye tissue, glandular tissue, and tongue tissue.

300. (New) The method of claim 263, wherein said cavity is selected from the group consisting of the lungs, the mouth, the nasal cavity, the stomach, the peritoneal cavity, the intestine, a heart chamber, veins, arteries, capillaries, lymphatic cavities, the uterine cavity, the vaginal cavity, the rectal cavity, joint cavities, ventricles in brain, spinal canal in spinal cord, and the ocular cavities.

H 1 cont'd

301. (New) The method of claim 263, wherein said cavity comprises a mucosal surface.

302. (New) The method of claim 300, wherein said mucosal surface is lung tissue.

303. (New) The method of claim 263, wherein said said administration is by a route selected from the group consisting of intravenous, intratracheal, intranasal, transdermal, intramuscular, interdermal, subcutaneous, intraocular, vaginal, rectal and inhalation.

304. (New) The method of claim 263, wherein said administration route is intravenous.

305. (New) The method of claim 304, wherein said administration route is intratracheal.

306. (New) The method of claim 304, wherein said administration route is intranasal.

307. (New) The method of claim 263, wherein said administration is mediated by a catheter.

A 1 cont'd

308. (New) The method of claim 263, wherein said administration is by injection.

309. (New) A method of reducing the amount of polynucleotide required to obtain a desired clinical response in a vertebrate, comprising administering to the vertebrate the composition of claim 263.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 58, 110, and 164-309 are pending in the application, with 1, 58, 110, 164, 216, and 263 being the independent claims. Claims 2-57, 59-109, 111-163 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 164-309 are sought to be added. It is believed that new claims 164-309 correspond to the subject matter of Group II, elected in the Reply to Restriction Requirement being submitted along with this Preliminary Amendment. Support for the new claims may be found in claims 1-163 as filed, and throughout the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Summary

It is respectfully believed that this application is now in condition for substantive examination. Early notice to this effect is respectfully requested

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

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Version with markings to show changes made

Claims 2-57, 59-109, 111-163 are canceled.

Claims 164-309 are new.